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SPECIAL SUPPLEMENT

Enzymatic Infarctions: How Important Are They, and How Do We Avoid Them?

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Stents Don't Require Systemic Anticoagulation....But the Technique (and Results) Must be Optimal

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Intracoronary stenting has gained widespread use over the last decade. This is largely due to accumulation of clinical trials with results demonstrating the superiority of stents over other catheter-based coronary interventions in regard to procedural predictability, reduced complications and improved long term efficacy.[1-3] In addition, intravascular ultrasound guidance of stent implantation has led to the concept of optimal stent deployment, a process that allowed coronary stenting to be performed safely without anticoagulation and with lower stent thrombosis and vascular complications.[4-6] The purpose of this communication is to summarize the present status of stent implantation without anticoagulation in concept and clinical utility.

Background. It has been clear from the initial experience of stent implantation in human coronary arteries[7] that acute or subacute thrombosis was a problem. In the European multicenter registry of the self-expanding Wallstent (105 patients) thrombosis occurred in 24% of patients.[8] In the multicenter clinical trial of Palmaz–Schatz stent[9], 983 patients underwent stenting of native coronary arteries with the Palmaz–Schatz stent in the United States. The first 67 patients in this series who were not treated with warfarin who were not treated with warfarin who were not treated with warfarin had a thrombosis rate of 11.9%. Other patients who were treated with warfarin for 1 month had an overall stent thrombosis of 5%. When stenting was used for bailout indications, stent thrombosis was much higher in spite of aggressive anticoagulation.[1,10,11] Even in the more recent prospective clinical trials on elective stenting, stent thrombosis was 3.5% in both the STRESS[2] and the BENESTENT[3] study. Those results were achieved despite vigorous anticoagulation that resulted in high vascular and bleeding complications. Vascular complications occurred in 10% and bleeding complications in 4.6% in the BENESTENT trial and in 7.4% in the STRESS trial.

Current status. Initial intravascular ultrasound observations during coronary stenting at our institution[4,5] have suggested that stent underexpansion was a common occurrence using the traditional stent deployment technique. In addition, it has

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been demonstrated in the same study that the use of larger balloons or higher pressures led to an increase in lumen cross section area. These observations led to the hypothesis that stent thrombosis was most probably a consequence of stent underexpansion, and that optimal coronary stenting with intravascular ultrasound guidance might decrease stent thrombosis without the need for anticoagulation. This hypothesis was tested in a prospective clinical trial enrolling 334 consecutive patients undergoing Palmaz–Schatz stent implantation. Routine high pressure balloon dilation was performed and intravascular ultrasound was used to document optimal stent expansion prior to post procedure treatment with only antiplatelet agents.[6] In this study the incidence of stent thrombosis at 1 month was 0.9%. The achievement of full stent expansion, complete stent apposition to the vessel wall and full lesion coverage was of fundamental importance in reducing the stent thrombosis rate without subsequent anticoagulation.

Other European studies on the use of reduced or no anticoagulation regimens after stent implantation reported low stent thrombosis rates using similar techniques for final stent optimization without intravascular ultrasound guidance. Morice et al. reported stent thrombosis in 1.7% and vascular or bleeding complications in 3.5% of 1250 patients treated with 1 month of ticlopidine and aspirin.[12] Baragan reported a 0.5% incidence of stent thrombosis and a 0.5% incidence of bleeding or vascular complications. These results were obtained in a cohort of patients pre–treated with ticlopidine 500 mg a day starting three days prior to stent implantation and continued for 1 month.[13] Goods reported incidence of stent thrombosis in 0.7% in 296 patients undergoing stenting with the Gianturco–Roubin stent.[14]

Technique and Results Must be Optimal. This evolution in coronary stenting is the result of improved stent deployment technique that led to restoration of lumen size and geometry providing a favorable milieu for laminar blood flow. However, in spite of optimal technique, occasionally intraprocedural complications arise, which if not corrected, might lead to stent thrombosis. Several factors have been identified to increase the risk of stent thrombosis in the era of low pressure stent deployment with anticoagulation. These factors included lack of anticoagulation, bailout stenting, small vessels, residual dissections, pre or post procedure thrombus and slow flow.[15,16] Preliminary data (unpublished) from our institution, in the era of high pressure stent deployment without anticoagulation, indicate that low ejection fraction, residual dissections or slow flow, multiple stents per lesion and smaller stent minimum lumen diameter post procedure were all predictors of stent thrombosis. However, in contrary to prior studies, bailout stenting per se was not predictive of stent thrombosis reflecting that the final result achieved is the key factor in determining predisposition to stent thrombosis. The common denominator is achieving a final optimal result.

What Constitutes Optimal Stent Deployment in the Present State of Knowledge? It is a physiologic fact that optimal coronary blood flow is dependent on the presence of normal epicardial vessels and normal microvascular bed. The ideal goal of catheter based coronary interventions is to restore the anatomy of epicardial coronary vessels, in dimensions and geometry, as close as possible to the normal state. Therefore, anatomical optimal stent deployment could be defined as a final arterial lumen with dimensions and geometry as close as possible to normal coronary artery. There is retrospective data[4-6] and preliminary prospective data[17] illustrating that intravascular ultrasound guidance is superior to angiography guidance in achieving optimal lumen dimensions and geometry. This would intuitively make intravascular ultrasound a superior technique to confirm optimal stent deployment using an anatomic definition.

However, in the current era of cost effectiveness, an argument could be made that optimal stent deployment should be defined based on clinical outcome. In that case, the question to be asked is whether optimal stent deployment based on an intravascular ultrasound confirmation leads to less procedural complications, less stent thrombosis and less restenosis compared to an approach using angiography for confirmation of optimal stent deployment. Prospective studies to answer the question are in process and a conclusive statement awaits the results of those trials. Therefore, we feel that until such data is available, an anatomic definition for optimal stent deployment should be utilized, particularly in high risk patients (low ejection fraction, small vessels, long lesions and bailout stenting).

Post stenting intravascular ultrasound is used to identify the adequacy of lesion coverage by the stent; occurrence of plaque prolapse and assessment of the parameters for optimal stent implantation. Such parameters include percent of stent expansion in regard to the reference lumen cross sectional area (minimum stent cross section area/average reference lumen corss section area, with an optimal value being $\geq 0.8\text{-}0.9$), symmetry (ratio of minimum/maximum stent diameter, with an optimal value > 0.7), and full stent apposition to the internal vessel wall or to the compressed plaque. These intravascular ultrasound criteria have been used to identify patients suitable for treatment with only antiplatelet agents post coronary stenting.[18-20]

What is The Optimal Stenting Technique? Optimal stenting technique is a lesion specific approach that integrates lesion morphology and location into the decision making process. This process includes the choice of the specific device or devices (in case of a need for adjunct debulking) to be used, in addition to the appropriate choice of balloon size, compliance and inflation pressure. These are all factors that are interactive and have a great importance in determining the success and the complications of a procedure. However, a balance should always be considered between the best possible result and the risk of clinical complications.[21] It is known that plaque composition alters plaque compliance[22] which in turn could alter the response of vessel wall to stretching under a given inflation pressure. Hence, preintervention intravascular ultrasound could be of great benefit in selected patients to assess lesion morphology (particularly presence of calcium), the extent of atherosclerotic disease and measurement of the reference vessel diameter to assist in device selection and balloon sizing. Our early experience with oversized balloons used to perform final stent dilation showed a significant increase in complications due to vessel rupture and dissection.[4] For these reasons we think that the final stent dilation should be performed with a noncompliant or minimal compliant balloon sized to the vessel to be treated. When we use a noncompliant balloon we may need a higher final inflation pressure compared to the one needed for the compliant balloon. Despite the need of a higher final pressure the noncompliant approach will add more safety and predictability to the procedure by avoiding overstretching the adjacent vessel segment. This technique does not require oversized balloons. The short balloon could also be of a distinct clinical utility particularly in situations where a satisfactory result is not achieved despite the use of an appropriately sized balloon inflated at high pressures. In this particular situation the use of an oversized short balloon seems rational and safe because it allows a more localized delivery of the dilating force in the segment needed and inside the stent. The degree of final inflation pressure should be judged in the context of lesion morphology and balloon size and compliance.

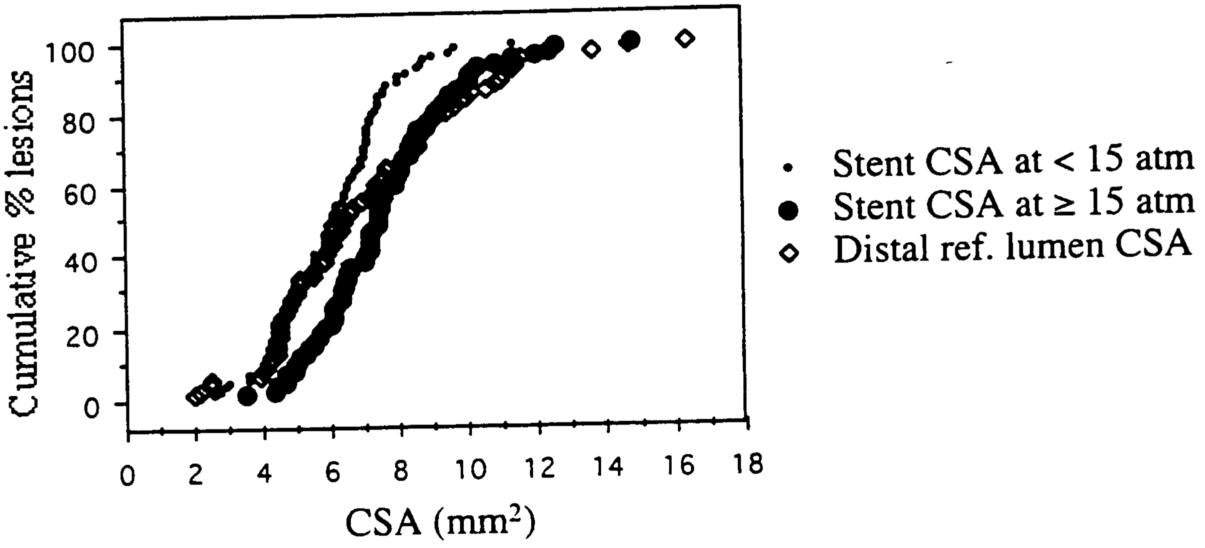

Figure 1. *A percentile curve illustrating the frequency distribution of minimal stent cross sectional area at intermediate inflation pressure and high pressure in relation to the distal reference lumen cross–sectional area.*

To address this question we analyzed data for 84 consecutive patients with 86 lesions undergoing intravascular ultrasound guided stent implantation. Noncompliant or semicompliant balloons were used with an initial inflation pressure < 15 atmospheres (mean 12 ± 2 atmospheres) and final inflation pressure of ≥ 15 atmospheres (mean 18 ± 1 atmospheres) without changing the balloon size. Mean balloon size was 3.5 ± 0.4 mm and B/V 1.13 ± 0.16. The tightest stent lumen cross sectional area increased from (6.06 ± 1.66 mm^2) at first inflation to (7.58 ± 2.06 mm^2) at final inflation ($p < 0.0001$). The final cross sectional area achieved was larger than the distal reference lumen cross sectional area 7.06 ± 2.89 mm^2 (Figure 1). No vessel perforation occurred in this cohort of patients. This retrospective analysis illustrates that a mean inflation pressure of 18 atmospheres and a mean B/V ratio 1 : 1 could be a safe and effective strategy to optimize stent expansion.

Does Post Procedure Antiplatelet Regimen Make a Difference? Although optimal stent expansion remains the single most important factor in reducing stent thrombosis, the appropriate post stent pharmacological regimen is still the subject of ongoing investigation and controversy. The issue is whether treatment with ticlopidine with adjunctive aspirin provides additive benefit over aspirin therapy alone after optimal stent expansion. There is an abundance of clinical evidence that supports the efficacy of ticlopidine based antiplatelet regimen after stent implantation.[12-14] However, there is minimal comparative clinical data to support the increased efficacy of this regimen compared to aspirin in an era of optimal stent implantation. We recently published a prospective randomized trial[23] involving 226 patients undergoing intravascular ultrasound guided coronary stenting. One hundred and three patients were randomized to aspirin alone and 123 patients to a combination of aspirin and ticlopidine. At 1 month the rate of stent thrombosis was 2.9% in the aspirin only group and 0.8% in the ticlopidine–aspirin group ($p = 0.2$). Cumulative major clinical events after successful stenting occurred in 3.9% of patients in the aspirin group and in 0.8% in the combined ticlopidine–aspirin group ($p = 0.1$). There were no medication side effects in the aspirin group; in the combined group, medication side effects occurred in 3 patients ($p = 0.2$)

The STARS (Stent Anticoagulation Regimen Study) trial[24] will provide further information on this issue. This randomized trial with over 1600 patients will evaluate the comparative benefit of three post stent drug regimens: aspirin and low dose warfarin; aspirin and ticlopidine; aspirin alone.

CONCLUSIONS

After nearly a decade of clinical investigation and use, the community of interventional cardiologists has come to agreement on the issue of stent thrombosis. It is recognized that stent thrombosis is, in large part, an event triggered by stent underexpansion and/or inflow and outflow obstruction. Therefore, it is of crucial importance to follow a good technique and to thrive to achieve the best results possible. However, we do recognize that controversy continues as to which is the best and most cost–effective technique to document achievement of optimal stent implantation. This issue awaits the results of ongoing prospective randomized clinical trials.

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